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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,091	07/15/2003	Steve Roffler	4910-2DIV2	8710

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,091	ROFFLER ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40-45 and 53* is/are allowed.

6)☒ Claim(s) *46-52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 2/23/2007 in response to the previous Non-Final Office Action (11/20/2006) is acknowledged and has been entered.

Claims 40-54 are currently pending and under consideration.

Objections Maintained:

Specification

The specification **remains** objected to as failing to provide proper antecedent basis for the claimed subject matter in claims 38 and 39. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

For each deposit made pursuant to the regulations for Deposit of Biological Material set forth in MPEP 1801, the specification shall contain:

(1) The accession number for the deposit;

(2) The date of the deposit;

(3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and

(4) The name and address of the depository.

New Rejections Necessitated by the Presentation of New claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a patient suffering from a tumor characterized as expressing a tumor associated (TAG-72) antigen, comprising the steps of: (a)

administering to the patient a polyethylene glycol containing compound consisting of B72.3-βG-PEG; 9b) administering to the patient after step (a) an anti-polyethylene glycol monoclonal antibody obtained via immunizing a mouse with an RH1-βG-PEG conjugate to accelerate the clearance of the polyethylene glycol-containing compound from the patents circulating blood; and (c) administering to the patient after step (b) a β-glucouronidase-activatable anti-tumor prodrug, does not reasonably provide enablement for a method of treating a patient suffering from any and/or all tumors, comprising the steps of: (a) administering to the patient a polyethylene glycol containing compound consisting of B72.3-βG-PEG; 9b) administering to the patient after step (a) an anti-polyethylene glycol monoclonal antibody obtained via immunizing a mouse with an RH1-βG-PEG conjugate to accelerate the clearance of the polyethylene glycol-containing compound from the patents circulating blood; and (c) administering to the patient after step (b) a β-glucouronidase-activatable anti-tumor prodrug; or administering in step (a) a polyethylene glycol containing compound comprising H25-βG-PEG. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of treating cancer in a mammal comprising administering an amount of a polyethylene glycol containing compound in combination with an antibody which clears said PEG containing compound and a β-glucouronidase-activatable anti-tumor prodrug. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating a patient suffering from a tumor, comprising the steps of: (a) administering to the patient a polyethylene glycol containing compound consisting of B72.3-βG-PEG or H25-βG-PEG; 9b) administering to the patient after step (a) an anti-polyethylene glycol monoclonal antibody obtained via immunizing a mouse with an RH1-βG-PEG conjugate to accelerate the clearance of the polyethylene glycol-containing compound from the patents circulating blood; and (c) administering to the patient after step (b) a β-glucouronidase-activatable anti-tumor prodrug. Thus, the claims encompass treating any and/or all tumors, as well as the administration of either a B72.3-βG-PEG conjugate or H25-βG-PEG conjugate, wherein a b-glucouronidase-activatable anti-tumor prodrug is activated by either conjugate. In other words, the claims encompass antibody directed enzyme prodrug therapy.

Guidance in the specification and Working Examples

The specification teaches that the present invention is directed to a method of treating cancer in a patient comprising administering a PEG-containing compound comprising a tumor targeting means and a means for activating an anti-tumor prodrug in a patient (page 9, lines 5-9). For example, the specification the specification teaches the therapy of LS174T xenografts, wherein a B72.3-βG-PEG conjugate or H25-βG-PEG conjugate, as the control, were administered to mice bearing LS174T tumors (page 48, lines 3+ and Figure 20A). In particular, the specification teaches that the mean size of tumors in mice treated with B72.3-βG-PEG was significantly smaller than the control (see Figure 20A). Moreover, the specification teaches the tumor localization of B72.3-βG-PEG conjugate or H25-βG-PEG conjugate, wherein B72.3-βG-PEG conjugate localized to the LS174T tumors and H25-βG-PEG did not (page 44, line 12+ and Figure 17). With regards to the B72.3 portion of the B72.3-βG-PEG conjugate, the specification teaches that mAb B72.3 is an IgG1 monoclonal antibody specific for the tumor-associated glycoprotein (TAG-72) antigen (page 17, lines 8-9). Wirth regards to the H25 portion of the H25-βG-PEG conjugate, the specification teaches that H25 is a control antibody that specifically binds to the surface antigen of hepatitis B virus (page 17, lines 9-11). Thus, while the specification reasonably conveys a correlation between inhibiting tumor growth and administration of a B72.3-βG-PEG conjugate, wherein B72.3 is a

monoclonal antibody specific for a tumor associated antigen, the specification does not appear to be commensurate in scope with the claimed invention because the claims encompass, in the alternative, a method of inhibiting tumor growth comprising a provide a correlation between tumor inhibition and administration of a H25-βG-PEG which is taught in the specification not to be effective (see figure 17 and 20A). While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with using antibody directed enzyme prodrug therapy.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that antibodies, which are useful in antibody directed enzyme prodrug therapy, should be directed to a tumor associated antigen. For example, Melton et al. (Journal of the National Cancer Institute 1996; 88: 153-165) teach that for any from of antibody mediated targeting to be successful, it is axiomatic that there must be selective expression of the target antigen by the tumor cells. Similarly, Jung et al. (Mini Reviews in Medicinal Chemistry 2001; 1: 399-407) teach that antibody directed enzyme prodrug therapy represents an interesting and promising form of targeted anticancer therapy because the antibody specifically targets an enzyme to the tumor cell and activates the prodrug solely at the tumor site (page 399, 1st column, 2nd paragraph). Thus, while considerable research has gone into developing this type of technology, the state of the prior art recognize that this technology revolves around the targeting specificity of the antibody to tumor cells.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlating the targeting efficacy/ in vivo inhibition of tumor growth with the H25-βG-PEG conjugate, and the

negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Claims 40-45 and 53 appear to be free of the prior art because the prior art does not appear to teach or suggest a method of accelerating the clearance of a polyethylene glycol compound from the circulating blood of a patient comprising administering an anti-polyethylene glycol monoclonal antibody.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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